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AUTOXIDATION OF BIOLOGICALLY ACTIVE AMINES
(June 1964 through June 1970)

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FINAL REPORT

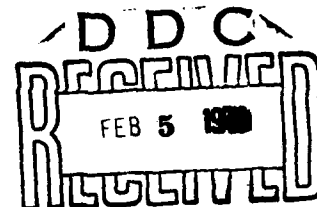
by

Jay K. Kochi
Hugh J. Williams
Elizabeth A. Singleton
Milton A. Ratcliff

December 1970



DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Physical Research Laboratory
Edgewood Arsenal, Maryland 21010



Contract DA18-035-AMC-272(A)

CASE WESTERN RESERVE UNIVERSITY
Department of Chemistry
University Circle
Cleveland, Ohio 44106

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Final Report

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DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Research Laboratories
Physical Research Laboratory
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Contract DA18-035-AMC-272(A)
Project 1C04501B71A

CASE WESTERN RESERVE UNIVERSITY
Department of Chemistry
University Circle
Cleveland, Ohio 44106

FOREWORD

The work described in this report was authorized under Project 1C04501B71A, Basic Research in Life Sciences. The work was started in June 1964 and completed in June 1970.

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DIGEST

The copper-catalyzed oxidation of amines was investigated using peresters as oxidants. Rather random cleavage of alkyl groups was found.

The autoxidation of N-alkyl isoindolines was found to be markedly enhanced by hydrogen donor solvents. A mechanism involving oxidative dehydrogenation to isoindoles followed by further rapid oxidation to phthalimidines was proposed.

The photochemical decomposition of benzylamine and a series of N-substituted benzylamines and benzylammonium salts was studied. Substituents included primary, secondary, and tertiary alkyl groups. Both the initial cleavage reaction and the primary dark reactions following bond cleavage were investigated. The primary, secondary, and tertiary amines were found to yield a benzyl radical and an amino radical during photolysis. No competition was observed for any alkyl group or hydrogen, leading to the conclusion that the photochemical reaction was a result of absorption in the aromatic chromophore. Product studies and labeling techniques showed the primary dark reaction, for secondary amines, to be one involving hydrogen atom abstraction by the amino radical from the N-H bond of a substrate molecule. Reactions involving these secondary amino radicals and benzyl radicals account for the majority of the other products.

AUTOXIDATION OF BIOLOGICALLY ACTIVE AMINES

I. INTRODUCTION.

The original intent of this contractual effort had been to discover and study systems for the catalyzed oxidation (and hopefully air oxidations) of amines. It was envisioned that the knowledge so gained would be of value in formulating catalytic systems to protect against biologically active amines. Initially, copper-catalyzed oxidations with peresters were examined by Kochi and Williams; these reactions were too slow to be of interest, except at high temperatures. Kochi and Singleton studied factors affecting the autoxidation (i.e., air oxidation) of N-alkyl isoindolines; this work was brought to a successful conclusion (Tetrahedron Letters, 24, 4649 (1968)), but proved to be a special case not likely to be of too much help in predicting the behavior of other amines. Finally, it was decided that an understanding of the free radical chemistry of amines was essential, and benzylamines were chosen as models by Kochi and Ratcliff.

II. RESULTS.

A. List of Reports.

The research conducted under this program has been summarized in reports as follows:

<u>Authors</u>	<u>Dates Covered</u>	<u>Date Issued</u>
Kochi & Williams	1 Oct 64 - 31 Jan 65	Jan 65
Kochi & Williams	31 Jan - 31 Mar 65	Apr 65
Kochi & Singleton	1 Apr - 30 Jun 65	Jul 65
Kochi & Williams	1 Apr - 5 Jul 65	Jul 65
Kochi & Singleton	1 Oct - 31 Dec 65	Jan 66
Kochi, Singleton & Williams	Oct 64 - Dec 65	Jun 66
Kochi & Singleton	Jan - Mar 66	Apr 66
Kochi & Singleton	1 Apr - 30 Jun 66	Jul 66
Kochi & Singleton	1 Jul - 30 Dec 66	
Kochi & Singleton	Apr 65 - Dec 66	May 67
Kochi & Singleton	1 Jan - 1 Jul 67	
Kochi & Singleton	Final Report	Sep 67
Kochi & Ratcliff	1 Feb - 31 May 68	Jun 68
Kochi & Ratcliff	1 Jun 68 - 31 Mar 69	Mar 69
Kochi & Ratcliff	1 Feb 69 - 30 May 69	Jun 69
Kochi & Ratcliff	Phase Report	Nov 70
	(1 Feb 68 - 30 Jun 70)	

B. Copper-catalyzed Oxidations with Peresters.

The copper-catalyzed oxidation of amines was investigated using peresters as oxidants. Rather random cleavage of alkyl groups was found.

C. Autoxidation of N-alkyl Isoindolines.

The autoxidation of N-alkyl isoindolines was found to be markedly enhanced by hydrogen donor solvents. A mechanism involving oxidative dehydrogenation to isoindoles followed by further rapid oxidation to phthalimidines was proposed.

D. Photochemistry of Benzylamines.

The photochemical decomposition of benzylamines and a series of N-substituted benzylamines and benzylammonium salts was studied. Substituents included primary, secondary, and tertiary alkyl groups. Both the initial cleavage reaction and the primary dark reactions following bond cleavage were investigated.

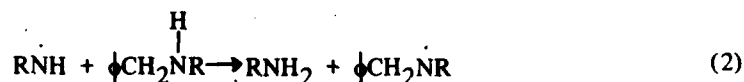
The primary, secondary, and tertiary amines were found to yield a benzyl radical and an amino radical during photolysis (eq. 1).



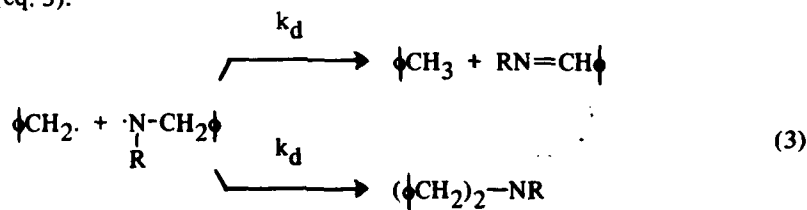
R = R' = H, benzyl, alkyl

No competition was observed for any alkyl group or hydrogen, leading to the conclusion that the photochemical reaction was a result of absorption in the aromatic chromophore.

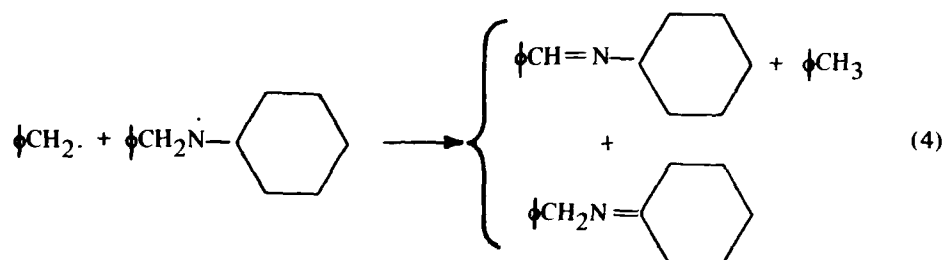
Product studies and labeling techniques showed the primary dark reaction, for secondary amines, to be one involving hydrogen atom abstraction from the N-H bond of a substrate molecule by the amino radical (eq. 2). Reactions involving these secondary amino radicals



and benzyl radicals accounted for the majority of the other products. Both the combination and disproportionation of a benzyl radical with an amino radical was observed, leading to a tertiary amine, toluene and an imine (eq. 3).



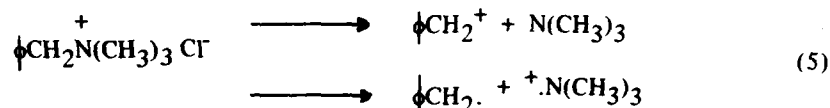
For the reaction of benzylcyclohexylamine, which yielded the benzylcyclohexylamino radical according to eq. 2, the disproportionation step of eq. 3 (k_d) was found to be competitive with respect to the direction of reaction (eq. 4). Both benzaldehyde and cyclohexanone



were obtained upon hydrolysis of the reaction mixture. For benzyl-*n*-hexylamine, the same effect was observed, although the ratio of benzaldehyde to hexanol was much greater.

The quantum yield for formation of benzylamine was studied under a variety of conditions in the photolysis of dibenzylamine. The results indicated that a combination of effects were operative. The quantum yield increased with increasing substrate concentration, indicating that scavenging of the radical pair was competing with secondary cage recombination. The decreased quantum yields with viscosity provided further support for this general tenet.

The decomposition of benzylammonium salts (primary, secondary, tertiary, and quaternary) was found to involve competing free radical and solvolytic pathways (eq. 5). Large amounts of ethers were obtained

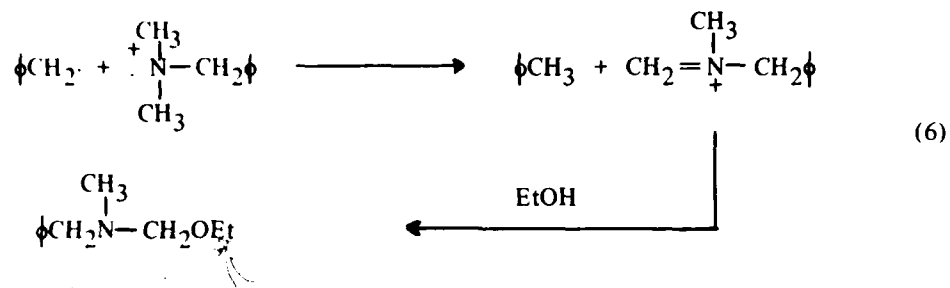


when the photolysis was carried out in methanol, ethanol, or *t*-butyl alcohol.

Substitution patterns revealed that an increase in steric effects (i.e., replacing methyl groups by benzyl groups) resulted in an increase in the ratio of solvolytic to free radical product.

While quaternary salts underwent ready decomposition, reducing the substitution by removing alkyl groups resulted in a net decrease in reactivity. This effect was greatest for benzylammonium chloride ($\phi\text{CH}_2\text{NH}_3^+ \text{Cl}^-$), which showed no photodecomposition even after extended irradiation.

Large amounts of toluene were observed and postulated to arise by cage disproportionation. The formation of formaldehyde and a secondary amine after hydrolysis were taken as additional evidence for the disproportionation mechanism (eq 6). Both of these products are expected from the hydrolysis of the α -aminoether formed by eq. 6.



Substitution patterns in the aromatic ring of benzyltrimethylammonium chloride showed that electron releasing groups in the meta position increase the rate of reaction as measured by quantum yields. Withdrawing groups meta retard the reaction while para substitution shows almost no effect.

III. CONCLUSION.

It may be concluded that this work has advanced the state of knowledge of amine oxidation chemistry and amine photochemistry, but that there is as yet no clue to the development of a general system that might catalyze the autoxidation of ordinary aliphatic amines.

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13. ABSTRACT <p>The copper-catalyzed oxidation of amines was investigated using peresters as oxidants. Rather random cleavage of alkyl groups was found. The autoxidation of N-alkyl isoindolines was found to be markedly enhanced by hydrogen donor solvents. A mechanism involving oxidative dehydrogenation to isoindoles followed by further rapid oxidation to phthalimidines was proposed. The photochemical decomposition of benzylamine and a series of N-substituted benzylamines and benzylammonium salts was studied. Substituents included primary, secondary, and tertiary alkyl groups. Both the initial cleavage reaction and the primary dark reactions following bond cleavage were investigated. The primary, secondary, and tertiary amines were found to yield a-benzyl radical and an amino radical during photolysis. No competition was observed for any alkyl group or hydrogen, leading to the conclusion that the photochemical reaction was a result of absorption in the aromatic chromophore. Product studies and labeling techniques showed the primary dark reaction for secondary amines to be one involving hydrogen atom abstraction by the amino radical from the N-H bond of a substrate molecule. Reactions involving these secondary amino radicals and benzyl radicals account for the majority of the other products.</p>		

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Alkyl radicals						
Amine oxidation						
Amines						
Autoxidation						
Benzylamines						
Benzylcyclohexylamine						
Benzyltrimethylammonium chloride						
Cage recombination						
Catalysis						
Copper						
Cupric ion						
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